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Natural history of childhood asthma

20-year follow-up

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SUMMARY Of 417 asthmatic children seen in hospital from 1941 to 1947, only 208 (50%) were still attending the hospital and were available for long-term follow-up, whereas a 91% follow-up was achieved from a personal follow-up of 267 asthmatic children seen in an East London group practice from 1948 to 1952 and followed for more than 20 years to December 1972. 125 patients (52%) were almost or completely symptom free; 51 (21%) had never had any symptom-free period for longer than 6 months; a further 63 (27%) had a remission of symptoms for 3 years before relapsing. 7 patients died, 3 due to their asthma.

The final prognosis was influenced by the severity of the asthma at onset, by breast feeding, by the presence of associated atopic disease, and by a positive family history of atopic disease in first-degree relatives. It was uninfluenced by the age of onset of the asthma, by the sex of the patients, or by skin testing results. Short-term follow-up of such patients will fail to include those patients whose asthma remits and subsequently relapses.

Much confusion still exists as to whether the long-term prognosis of childhood asthma is affected by breast feeding, early age of onset, severity of the asthma at onset, family history of atopic disease, presence of associated atopic disease or of positive prick skin test results to external allergens. In order to resolve these problems, a long-term follow-up of asthmatic children under 12 years of age attending hospital was started in 1941 and continued to 1947, by which time only 208 (50%) of the original 417 were still attending hospital. These were followed up till 1969 (Blair, 1969).

It was felt that a more satisfactory study could be obtained by a personal prospective follow-up from general practice. Of 267 asthmatic children under 12 years of age, seen between the years 1948 to 1952, 244 (91·4%) were followed till 1972.

Patients and methods

The definition adopted of asthma in childhood was of recurrent attacks of paroxysmal dyspnoea with wheezing. No attempt was made to differentiate between 'asthmatic bronchitis', 'bronchitic asthma', 'bronchial asthma', and 'asthma'. The only criterion for diagnosis was that the child had a minimum of three attacks of paroxysmal dyspnoea with wheezing.

The following details were recorded for each asthmatic studied: date of birth; birthweight; feeding history; history of atopic disease in the patient and family; the home conditions especially of the bedroom; patient's height and weight when first seen; the results of full clinical examination, blood tests; prick skin test to the commoner external allergens; and chest *x*-ray. The patients were seen frequently until they were symptom free and then annually. For those asthmatics moving from the area of practice, arrangements were made for their follow-up to be maintained either by mail, telephone, through a relative in the area of practice, or by attendence at hospital annually (with the co-operation of their new family doctors). Occasionally contact was lost but was re-established either with the help of old neighbours or with the assistance of the Records Department of the Executive Council (Family Practitioner Committee) of the National Health Service.

The severity of asthma in the first years of follow-up was classified as either (i) *mild* – not more than three attacks a year, each not incapacitating the patient sufficiently to be kept home from school, the attacks responding to bronchodilators only, and clearing within 1 to 3 days, or (ii) *severe* – more than three attacks a year, some of which required hospitalization or persisted for 5 days or more, incapacitating the child and necessitating some absences from school.

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At the end of follow-up in 1972, to assist in their analyses, the patients were classified as follows. (A) *No asthma* – patients living normal lives, being asymptomatic for a minimum period of 2 years. (B) *Mild asthma* – patients living a normal life with symptoms easily controllable and not requiring absences from school or work. These patients did not, as a rule, admit to having asthma on a questionnaire. They were only traced by personal interview (Blair, 1974). (C) *Chronic asthma* – patients living a fairly normal life. They have never been clear of asthma for any prolonged period (6 months or more). They require frequent bronchodilator administration orally or by aerosol and have occasional severe attacks, some requiring absences from school or work or hospitalization. (D) *Recurrent asthma* – those patients who, though completely asymptomatic for a minimum period of 3 years, had relapsed. (Such patients are missed in short-term follow-ups.)

Results

At the start of the study (1948–1952) the mean number of registered persons in the group practice was 6909 (3300 males, 3609 females – ratio 1–1·1). At the end of the study (1972) the number of registered persons in the practice was 9145 (4433 males, 4712 females – ratio 1–1·1).

The age and sex distribution in the group practice (mean figures for 1948 and 1952) and at the end of the study (1972) and of the population of England and Wales (Registrar-General's figures for England and Wales 1951, 1971) were approximately the same, with a preponderance of females in the entire practice and total population groups and a preponderance of males of 0 to 20 years of age (Table 1). The census figures for 1951 were the first available since 1931. There was a preponderance of females in the entire practice and total population groups and a preponderance of males in all the 0- to 20-year age groups.

Age at which asthmatics were first seen. All the asthmatic children were seen within a year of onset of symptoms. At the start of the study there were 211 asthmatics under 12 years of age: 104 (50%) were aged up to 5 years, 70 (33%) between 6 and 9 years, and 37 (17%) between 10 and 12 years. 56 new asthmatics were admitted to the study from 1948 to 1952; 32 under 5 years and 24 between 6 and 9 years. Of these 267 asthmatics, 23 could no longer be traced. These were all in the under-5 age group in 1948 and were excluded from the analysis. Therefore 244 (91·4%) patients were studied.

During the first 5 years of follow-up these 244 patients were subdivided into *mild asthma* 118 (49%) and *severe asthma* 126 (51%). On completion of the study on 31 December 1972, 68 (28%) patients were asymptomatic for a minimum of 2 years—(*no asthma* group), 59 (24%) had minimal symptoms—(*mild asthma* group), 114 (48%) had symptoms which necessitated either periodic absences from work or hospitalization, 51 (21%) had had no period of freedom longer than 6 months—(*chronic asthma* group), and a further 63 (27%) patients had a remission for 3 years and then relapsed—(*recurrent asthma* group).

The average duration of the asthma in the *no asthma* group was 6 years (range 2–18 years). In the

Table 1 *Age and sex distribution of the group practice in 1950 (mean figures of 1948–1952) and in 1972 compared with the Registrar General's figures for England and Wales in 1951 and 1971*

Date	*Series*	*Age in years*	*No.*	%	*Sex*			
					Male	%	*Female*	%
July 1950	Entire	0–90+	6909		3300	48	3609	52
Mean of the	practice	0–20	2085	30	1064	51	1021	49
1948 to 1952		5–15 (school-children	973	14				
figures								
Dec. 1972	Entire	0–90+	9145		4433	48	4712	52
End of study	practice	0–20	2800	31	1489	53	1311	47
		5–15 (school-children)	1354	15				
1951 census	Population	0–90+	44·46		21·34	48	22·86	52
	(in millions)	0–20	12·56	28	6·39	51	6·16	49
		0–15 (school-children)	6·99	16				
1971 census	Population	0–90+	48·5		23·5	48·5	25	51·5
	(in millions)	0–20	14·9	31	7·6	53	7·3	47
		5–15 (school-children)	7·6	16				

recurrent asthma group the average duration of the asthma before remission was 10 years (range 3–18 years)—the average duration of the remission was 9 years (range 3–15 years) and the average age of relapse was 18 years.

The factors which could influence the prognosis of childhood asthma were compared for the first 5 years of follow-up for *mild* and *severe* asthma, and on completion for the *no asthma/mild asthma* group and the *chronic/recurrent asthma* group of patients, calculating the χ^2 value.

Age of onset. There was no correlation between an early age of onset and severity of asthma either during the first 5 years of follow-up or with its persistence after the 20 years' follow-up (Table 2).

Table 2 *Age of onset and incidence of asthma in the first 5 years and after 20 years of follow-np*

State of asthma	*Age of onset (years)*							
	<2		*2–5*		*>5*		*Total*	
	n	%	*n*	%	*n*	%	*n*	%
In first 5 years of study								
Mild	61	44	36	55	21	54	118	48
Severe	78	56	30	45	18	46	126	52
Total	139		66		39		244	
End of study								
No asthma/ mild asthma	69	50	36	56	18	50	123	52
Chronic/ recurrent asthma	68	50	28	44	18	50	114	48
Total	137		64		36		237	

Sex. The sex of the patient did not affect the severity of asthma at the onset (males—*mild* to *severe*, 65 to 76 (46 to 54%); females 53 to 50 (51 to 49%)), nor did it affect the ultimate prognosis (males 74 to 62 (54 to 46%); females 49 to 52 (49 to 51%)) ($\chi^2=0\cdot59$, $P=0\cdot5$).

Breast feeding (Table 3). Breast feeding, up to a week, improved the early prognosis for childhood asthma ($P=0\cdot01$) comparing the *mild* and *severe onset* asthma groups, but on long-term follow-up this improvement was marginal ($\chi^2=2\cdot49$) comparing the *no asthma/mild asthma* and the *chronic/recurrent* asthma groups. With breast feeding for 8 weeks or more, $\chi^2=4\cdot47$, $P<0\cdot05$. This was significant at 5% at all stages.

History or presence of atopic disease in the patient. In the early years the history or the presence of infantile eczema did not affect the severity of the asthma, whereas in the final analysis the presence of associated persistent eczema was highly significant ($\chi^2=25\cdot3$, $P<0\cdot001$), indicating a severe and persistent asthma (Table 4).

Rhinitis, whether perennial or seasonal, aggravated the prognosis at all stages. In the first 5 years, $P<0\cdot01$, and on completion of the study, $P<0\cdot005$, $\chi^2=9\cdot88$.

Family history of atopic disease. A family history of atopic disease in their first-degree relatives was highly significant at all stages in determining prognosis ($P<0\cdot001$) (Table 5).

Skin tests. In the early stages of follow-up, positive prick skin test results were highly significant indicating a more severe form of asthma ($P=0\cdot01$). In *mild asthma*—single prick skin tests were positive in 22 (37%); multiple prick skin tests were positive in 38 (41%), but with *severe onset* asthma the corresponding figures were 38 (73%) and 55 (59%). But on completion of the study, the prick skin test results did not affect the prognosis (χ^2 very nearly 0).

Length of follow-up. The incidence of *no asthma/ mild asthma* patients increased with the length of follow-up (Table 6). Remissions occurred between the 5- and 10-year follow-up analysis. The average age at which relapse occurred was 18 years.

Table 3 *Incidence of breast feeding in patients with childhood asthma*

State of asthma	*Breast feeding*					
	Nil		*Maximum of 1 week*		*More than 8 weeks*	
	No.	%	*No.*	%	*No.*	%
In first 5 years of study						
Mild	18	31	27	69	58	72
Severe	41	69	12	31	22	28
Total	59		39 $P=0\cdot01$		80 $P=0\cdot01$	
End of study						
No asthma/mild asthma	21	36	21	54	60	75
Chronic/recurrent asthma	38	64	18	46	20	25
Total	59		39 $\chi^2=2\cdot49$		80 $\chi^2=4\cdot47$, $P<0\cdot05$	

Table 4 *Presence or history of atopic diseases and incidence of asthma in the first 5 years and after 20 years of follow-up*

State of asthma	Disease											
	Infantile eczema				Seasonal rhinitis				Perennial rhinitis			
	Cleared completely		Still persisting		Alone		With seasonal asthma		Alone		With seasonal asthma	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
In first 5 years of study												
Mild	30	41							20	32		
Severe	44	59							42	68		
Total	74								62			
End of study												
No asthma/mild asthma	30	73	4	12	26	67	18	49	18	29	44	57
Chronic/recurrent asthma	11	27	29	88	13	33	19	51	44	71	33	43
Total	41		33		39		37		62		77	

Table 5 *Incidence of asthma and history of atopic disease in first- and second-degree relatives*

State of asthma	Family relationship					
	First-degree relatives		Second-degree relatives		Total	
	n	%	*n*	%	*n*	%
In first 5 years of study						
Mild	23	29	9	35	32	30
Severe	56	71	17	65	73	70
Total	79		26		105	
End of study						
No asthma/ mild asthma	20	27	13	43	33	31
Chronic/ recurrent asthma	55	73	17	57	72	69
Total	75		30		105	

Severity of asthma at onset (Table 7). *Severe onset* asthma predisposed significantly ($P<0{\cdot}001$) to *chronic* asthma. *Recurrent* asthma was unrelated to the initial severity. The 3 asthmatic deaths of the series were all in the *severe onset* asthma group.

Blood examinations. A mild secondary anaemia occurred in 8 patients (3%). Eosinophilia (>400/mm^3) was present in 48 patients (20%) examined in a well-controlled phase of the asthmatic state, and in 63 of 119 examinations (55%) made during an acute attack of asthma. Eosinophilia >1000/mm^3 was present in 2 patients with associated generalized prurigo and ichthyosis.

Nasal smears. These were examined for nasal eosinophilia as a routine during the first 5 years but yielded no additional information and were discontinued. Smear tests were positive for eosinophilia in patients with associated seasonal rhinitis and also in patients with perennial rhinitis whose dust sensitivity was confirmed by positive prick skin tests.

Table 6 *Incidence and grades of severity of asthma associated with length of follow-up*

No. of years of follow-up	Groups											
	Asymptomatic for 2 years or more		Mild		Severe		Chronic		Recurrent		Death	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
After 5 years	36 (21 of mild asthma; 15 of severe asthma)	15	97	40	111	45						
After 10 years	84 (58 of mild asthma; 26 of severe asthma)	35	60	25			90	27	8	3	2(A)	1
After 20 years	66	28	57	24			51	21	63	27	7 (4 NA 3 A)	2

A=asthmatic death; NA=nonasthmatic death.

Table 7 *Final severity of 244 asthmatic children after 20 years' follow-up related to initial severity*

Severity							
	Final						
						Total deaths	
Initial	*No asthma*	*Mild asthma*	*Recurrent asthma*	*Chronic asthma*	*Total*	*Non-asthmatic*	*Asthmatic*
Mild (118)	41	40	30	3	114	4	0
Severe (126)	25	17	33	48	123	0	3
Total (244)	66	57	63	51	237	4	3
P	0·05	<0·05	Not significant	<0·001			

Discussion

Childhood asthma can no longer be thought of as an unpleasant burden to be borne for a limited time after which all will be well. It is a killing disease, as Jacoby stated in 1966. An annual average death rate of 101 children under 15 years of age was recorded from 1961 to 1963 by the Registrar General, with a further 201 deaths between the ages of 15 and 30 years. In the latter group most, if not all, developed asthma in childhood. The mortality from childhood asthma increased sevenfold between 1956 and 1966 in the 10- to 14-year age group, according to Speizer *et al.* (1968). Although the abuse of bronchodilator aerosols has been stopped, mortality has not returned to the pre-1959 level, state Inman and Adelstein (1969). These changes in mortality rate were not reflected in this series, possibly as bronchodilator aerosols were rarely prescribed and then only with explicit instructions as to their use and abuse.

The asthma mortality in this series was 1·2% (3 deaths in a 20-year study of 244 asthmatic children). The mortality in other published series varies from 0·5% (Wilken-Jensen, 1963) to 6·1% (Pearson, 1967) over a 6- to 30-year follow-up.

Early age of onset. The age of onset of asthma in this series was under one year in 95 patients (39%), under 2 years in 139 (57%), and under 5 years in 205 (84%). An early age of onset is characteristic of all the series of asthma in childhood. Early age of onset indicated a more favourable prognosis according to Flensborg (1945), Rackemman and Edwards (1952), Smith (1961), and Ogilvie (1962), but a worse prognosis according to Bray (1930; 1937), Williams and McNicol (1969), and McNicol and Williams (1973), and no effect on the prognosis according to Wilken-Jensen (1963), Barr and Logan (1964), and Johnstone and Dutton (1968). In this series early age of onset did not affect the prognosis at any stage.

Effect of sex. The prognosis was better in boys than in girls according to Bray (1937), Rackemann and Edwards (1952), Smith (1961), and Pearson (1967), whereas Ogilvie (1962) and Johnstone (1968) did not consider that sex affected the prognosis at any stage. The sex incidence in Dawson *et al.*'s 1969 series varied from 1·3 to 3·3 males to 1 female according to the age of onset of their asthma, whereas Bray (1937) reported an incidence of 2 males to 1 female. In this series the ratio of males to females was 1·4 to 1; sex did not affect the long-term prognosis.

Family history of atopic disease. In this series the initial and final prognosis was affected significantly by a positive family history of atopic disease in first-degree relatives only.

History or presence of associated atopic disease. The two atopic diseases included at the start were perennial rhinitis and infantile eczema, as none of the patients had as yet developed seasonal rhinitis (this was included in the final analysis). Bullen (1929), Bray (1937), and Barr and Logan (1964) indicated in their results that associated infantile eczema was of bad prognostic significance. This was confirmed in this series. Witts (1936), however, stated that its presence bore no relationship to the ultimate prognosis. Associated perennial and/or seasonal rhinitis in this series was highly significant at all stages ($P<0·01$ during the first 5 years, and $P<0·005$ at the end of the study).

Breast feeding. Grulee and Sanford (1936) reported that breast-fed infants had a sevenfold protection from allergic disease. This beneficial effect was confirmed in this series: the early prognosis bene-

fiting from breast feeding up to one week, but for long-term prognostic improvement breast feeding for longer periods (>8 weeks) was necessary.

Skin tests. Positive prick skin test results indicated a more severe onset asthma ($P<0\cdot01$) but this did not affect the long-term prognosis.

Length of follow-up. Salter (1860), Unger (1935-36), Bray (1937), Smith (1961), and Barr and Logan (1964) reported that prognosis for childhood asthma improved with puberty. Unger (1935-36), Rackemann and Edwards (1952), Pearson (1958), Oswald and Fry (1962), and Altounyan (1972) described, as in this series, patients with remissions and subsequent relapse of asthma. Follow-up series of less than 10 years and not continuing after 18 years of age (the average age of relapse in this series) give a false impression of the true natural history of childhood asthma. Personal interviews are necessary in tracing mild asthmatics as they often fail to reveal their symptoms on a questionnaire (Blair, 1974).

In this series, as in the McNicol and Williams (1973) report of their findings of a 7-year follow-up study of 315 children with asthma, *severe onset* asthma predisposed to persistence of the asthma. 48% of children with asthma, whose onset was under 12 years of age, had not outgrown their asthma 20 years later. 21% had never stopped wheezing for any period longer than 6 months and 27%, though having had remissions of 3 years or more, had relapsed.

Buffum and Settipane (1966) reported on 518 patients (72% of a retrospective follow-up of 722 asthmatic children originally seen before 1956 and followed up for 10 years; 136 (26%) were followed-up for a further 10 years). 41% were well and only 5·6% severely handicapped at the first follow-up, while 55·1% were well and 5·1% severely handicapped at the second follow-up. These results are difficult to compare with the present series as the categories are defined differently.

Conclusion

The natural history of childhood asthma can be best determined by a long-term prospective follow-up. Early recognition of the factors which influence the long-term prognosis will indicate those asthmatic children in whom a concentrated effort will be required to improve the final prognosis.

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